

I. Epidemiology and genetics of asthma

Prevalence and etiology of asthma

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An increased understanding of the causes of asthma is coming from the international comparisons of asthma prevalence, particularly those from the European Community Respiratory Health Survey of asthma prevalence in adults and the International Study of Asthma and Allergies in Childhood. From these and other studies of asthma prevalence, it is possible to draw some tentative conclusions as to the patterns of asthma prevalence worldwide. There are five striking patterns: first, asthma prevalence is increasing worldwide; second, asthma is generally more common in Western countries and less common in developing countries; third, asthma is more prevalent in English-speaking countries; fourth, asthma prevalence is increasing in developing countries as they become more Westernized or communities become urbanized; and fifth, the prevalence of other allergic disorders may also be increasing worldwide. These five key features of the international patterns of asthma prevalence raise major questions about the role of "established" risk factors for the development of asthma. As a result, recent research has expanded to include the study of novel factors that may "program" the initial susceptibility to sensitization or contribute to the development of asthma independent of atopic sensitization. These include various exposures in utero, which are reflected in various perinatal factors measured at birth, and exposures (or lack of exposures) in the early years of life that may make the infant more susceptible to the subsequent development of asthma. These issues are now the focus of an intensive research effort worldwide, and the next few years are likely to see exciting advances in our understanding of the causes of asthma. (*J Allergy Clin Immunol* 2000;105:S466-72.)

Key words: Asthma, prevalence, atopic disorders, ISAAC, etiology

In the past, a significant contribution of epidemiology to the study of cancer, cardiovascular disease, and other chronic disorders has included analyses of patterns of disease prevalence and incidence across demographic groups, geographic areas, and across time (variation by "person, place and time"). In particular, many of the epidemiologic hypotheses concerning the causes of chronic disease have stemmed, at least in part, from international

Abbreviations used

ECRHS: European Community Respiratory Health Survey
ISAAC: International Study of Asthma and Allergies in Childhood

comparisons.¹ However, standardized international comparisons of asthma prevalence had not been conducted until recently. In this respect, the epidemiology of asthma is currently in a situation similar to that of cancer epidemiology or cardiovascular disease epidemiology before the major advances in understanding of the causes of these diseases in the 1960s. In this report, we discuss the importance of international comparisons of asthma prevalence, review what is already known from such comparisons, and discuss the implications for future etiologic research.

IMPORTANCE OF GLOBAL COMPARISONS

The value of international comparisons is well established in other fields of epidemiology. For example, many of the recent discoveries of the causes of cancer (including dietary factors and colon cancer, hepatitis B and liver cancer, aflatoxins and liver cancer, human papilloma virus and cervical cancer) have their origins, directly or indirectly, in the systematic international comparisons of cancer incidence conducted in the 1950s and 1960s.² These revealed that there were major international differences in cancer incidence, particularly between industrialized countries and the developing world. These international patterns suggested hypotheses concerning the possible causes of these patterns, which were investigated in more depth in further studies. In some instances these hypotheses were consistent with biological knowledge at the time and might have been advanced at some stage even if the international comparisons had not been made. However, in other instances, the epidemiologic hypotheses that were suggested were new and striking and might not have been proposed or might not have been investigated further if the international comparisons had not been made.

The same logic applies to epidemiologic studies involving comparisons within populations. For example, of the 30 to 40 known occupational causes of cancer,³ almost all were apparently first "discovered" in clinical case reports and epidemiologic studies⁴; none was first discovered in the laboratory, and in some instances (eg, arsenic, benzene) it took many years of laboratory research to support the epidemiologic findings and to establish the etiologic mechanisms involved.

It is also notable that the striking international differ-

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ences in cancer incidence may not have been apparent if the cancer incidence analyses had been confined to countries with similar lifestyles, as the differences in cancer incidence (and in the lifestyle-related risk factors that cause the incidence patterns) in many instances would not have been sufficiently great. More generally, Rose^{5,6} has noted that whole populations or regions of the world may be exposed to risk factors for disease (eg, high levels of cholesterol and/or low dietary levels of antioxidants), and the associations of these factors with disease may only be apparent when comparisons are made between populations rather than within populations.

Strategies for international comparisons

International and regional asthma prevalence comparisons are required as a key step in ascertaining the causes of asthma. However, such comparisons are not straightforward because epidemiologic surveys of asthma prevalence require large numbers and high response rates to obtain valid information. For example, asthma prevalence surveys typically require a minimum of 1000 persons, and ideally 3000 persons, with a response rate of greater than 90% to estimate asthma prevalence and severity with reasonable precision.⁷ It is also important that the information is obtained in a comparable manner across all participating centers and countries and that problems of translation of questionnaires and other problems of noncomparability of information are minimized.

Thus the main objective is to gain comparable information on asthma prevalence on the largest possible number of people in random population samples. This is quite different from the clinical situation, in which the aim is to gain the maximum possible information on a single patient. Such clinical considerations have often led to asthma prevalence surveys involving a number of sophisticated, expensive, and time-consuming tests on a small number of people. Such methods may collect good information on the small number of study subjects, but they are of little value in prevalence comparisons because of their small numbers, low response rates, and the usual problems of possible noncomparability of methods across countries and regions.

For these reasons, comparisons of asthma prevalence are increasingly being based on a simple comparison of symptom prevalence in a questionnaire survey of a large number of people, followed by more intensive testing of factors related to asthma (bronchial hyperresponsiveness, lung function) and risk factors for asthma (atopy, serum IgE, and other exposures) in a subsample. This approach has been used in the European Community Respiratory Health Survey (ECRHS) of asthma prevalence in adults⁸ and in the International Study of Asthma and Allergies in Childhood (ISAAC).⁷

European Community Respiratory Health Survey

The ECRHS⁸ had as objectives: (1) to determine the variation in the prevalence of asthma, asthma-like symptoms, and bronchial lability in Europe, (2) to estimate

TABLE I. ECRHS and ISAAC phase I study designs

	ISAAC, 6-7 years	ISAAC, 13-14 years	ECRHS, 20-44 years
Sample size	3000	3000	3000
Information source	Parents	Self-reported	Self-reported
Asthma written questionnaire	Strongly recommended	Compulsory	Compulsory
Asthma video questionnaire	Not used	Strongly recommended	Not used
Rhinitis written questionnaire	Strongly recommended	Compulsory	Single Question
Eczema written questionnaire	Strongly recommended	Compulsory	Not used

variation in exposure to known or suspected risk factors for asthma; to measure their association with asthma; and to further assess the extent to which they may explain variations in prevalence across Europe, and (3) to estimate the variation in treatment practice for asthma in the European community.

In each center a representative sample of 3000 adults, 20 to 44 years of age, completed a phase I screening questionnaire seeking information on asthma symptoms and medication use (Table I). Individuals answering "yes" to waking with an attack of shortness of breath in the last 12 months, an attack of asthma in the last 12 months, or taking current asthma medications were defined as "asthmatic." A random subsample of 600 subjects and an additional sample of up to 150 "asthmatic" individuals were then studied in more detail in phase II, with measurements of skin prick test to common allergens, serum total and specific IgE, bronchial responsiveness to inhaled methacholine and urine electrolytes, and an additional questionnaire on asthma symptoms and medical history, occupation and social status, smoking, the home environment, and the use of medications and medical services.

The phase I results⁹ include data from 48 centers in 22 countries, predominantly in Western Europe, with 9 centers from 6 countries outside Europe. The study found a wide variation in asthma symptom prevalence (Table II). The lowest prevalence rates were from India and Algeria, followed by centers from Italy, France, Belgium, and Germany. The highest prevalence rates were predominantly from centers in the British Isles, New Zealand, Australia, and the United States (ie, in English-speaking countries).

International Study of Asthma and Allergies in Childhood

The ISAAC⁷ had as objectives: (1) to describe the prevalence and severity of asthma, rhinitis, and eczema in children living in different centers and to make comparisons within and between countries, (2) to obtain baseline measures for assessment of future trends in the prevalence and severity of these diseases, and (3) to provide a framework for further etiologic research into lifestyle, environmental, genetic, and medical care factors affecting these diseases.

TABLE II. ECRHS: Prevalence of self-reported wheeze in previous 12 months in adults 20 to 44 years of age (%)

Country	No. of Centers	Prevalence (%)	
		Mean	Range
India	1	4.1	—
Algeria	1	4.2	—
Italy	3	10.0	8.5–10.7
Austria	1	14.3	—
France	5	14.7	13.6–15.7
Greece	1	16.0	—
Belgium	2	16.6	12.8–20.6
Switzerland	1	16.9	—
Germany	2	17.2	13.3–21.1
Iceland	1	18.0	—
Portugal	2	18.3	17.7–19.0
Netherlands	3	20.6	19.7–21.1
Sweden	3	20.7	19.2–23.2
Spain	6	22.0	16.2–29.2
Denmark	1	24.1	—
Norway	1	24.6	—
England	3	25.4	25.2–25.7
United States	1	25.7	—
New Zealand	4	26.8	24.2–27.3
Estonia	1	26.8	—
Scotland	1	28.4	—
Ireland	2	28.7	24.0–32.0
Australia	1	28.8	—
Wales	1	29.8	—

The ISAAC study has a study design similar to that of the ECRHS study. However, the emphasis is on obtaining the maximum possible participation across the world to obtain a global overview of asthma symptom prevalence in children. For this reason the questionnaire modules have been designed to be simple and to require minimal resources to administer. In addition, a video questionnaire involving the audio-visual presentation of clinical signs and symptoms of asthma has also been developed¹⁰⁻¹² to minimize translation problems. Furthermore, to maximize participation of centers around the world, phase I and phase II have been separated and need not be performed in the same groups of children (in fact, phase II is optional).

The characteristics of phase I of the ISAAC study are summarized and contrasted with the ECRHS in Table I. The population of interest is schoolchildren 6 to 7 years of age and 13 to 14 years of age within specified geographical areas. The older age group was chosen to reflect the period when morbidity from asthma is common and to enable the use of self-completed questionnaires. The younger age group was chosen to give a reflection of the early childhood years and involves completion of questionnaires by the parents.

The preliminary results, covering approximately 120 centers in 50 countries and involving more than 500,000 children, showed striking international differences in asthma symptom prevalence. The prevalence of self-reported wheezing in the previous 12 months in 13- to 14-year-old children varied from 1.9% to 35.3% in different centers.¹³ The corresponding figures for the 6- to 7-year-old age group was 1.6% to 27.2%.¹³ By using

both the written and video questionnaires, the highest prevalence rates were from English-speaking countries, with the low prevalence rates observed from centers in Eastern Europe and most developing countries.¹⁴⁻¹⁶

WHAT DO WE ALREADY KNOW FROM INTERNATIONAL COMPARISONS?

From the initial publications of the ECRHS program, the abstracts reporting the preliminary ISAAC analyses, and other asthma prevalence studies, it is possible to draw some tentative conclusions as to the patterns of asthma prevalence worldwide.

Asthma prevalence is increasing worldwide

The first key pattern is that the prevalence of asthma is increasing worldwide.¹⁷⁻²⁰ Most studies that have determined the prevalence of asthma symptoms by using the same methodology in the same community at different times have reported that asthma prevalence has increased in recent decades and that the magnitude of the increase has in some cases been substantial (Table III).²¹⁻⁴¹ Although methodological differences in these studies make it difficult to compare the magnitude of the differences in asthma prevalence between countries, the trend of increasing prevalence among populations in countries of widely differing lifestyles and ethnic groups is generally consistent.

Asthma is more prevalent in Western countries

The second pattern is that asthma prevalence is generally higher in Western countries than in developing countries. This pattern is illustrated by the ECRHS findings in which the rates for "wheezing in the last year" are considered. The median prevalence for the ECRHS study was 20.7%, with a range in the Western countries of 8.5% (Pavia) to 32.0% (Dublin). However, the prevalence was 4.2% in Algiers and 4.1% in Bombay.

Similar observations were made in the preliminary report of the ISAAC findings from the Southeast Asian region (Table IV).⁴² Centers with the lowest prevalence of asthma symptoms came from China (3.1% to 5.1%), with the highest rates for the region in Japan (13.2%) and Hong Kong (12.4%). These differences are unlikely to be caused by problems associated with the administration of the written questionnaire in different languages, as similar patterns were observed when the video questionnaire was used. Furthermore, 4-fold differences were observed in the prevalence of asthma symptoms between Guangzhou and Hong Kong, areas that are very close geographically, have the same predominant ethnic group, and use the same written language.

The highest asthma prevalence rates are in English-speaking countries

The third pattern is that English-speaking countries have the highest asthma symptom prevalence rates. From the ECRHS study the authors commented that although

TABLE III. Changes in prevalence of asthma or asthma symptoms in children and young adults

Country	Period	Prevalence		Reference
		1st Study (%)	2nd Study (%)	
Australia	1982-1992	5.6	10.5	Peat et al (1994) ²¹
Canada	1980-1983	3.8	6.5	Infante-Rivard et al (1987) ²²
England	1956-1975	1.8	6.3	Morrison Smith (1976) ²³
	1966-1990	3.9	6.1	Whincup et al (1993) ²⁴
Finland	1961-1986	0.1	1.8	Haahela et al (1990) ²⁵
France	1968-1982	3.3	5.4	Perdrizet et al (1987) ²⁶
Hong Kong	1989-1994	4.6	7.6	Lai et al (1997) ²⁷
Israel	1986-1990	7.9	9.6	Auerbach et al (1993) ²⁸
Japan	1982-1992	3.3	4.6	Nishima (1993) ²⁹
New Zealand	1969-1982	7.1	13.5	Mitchell (1983) ³⁰
	1975-1989	7.9	13.3	Shaw et al (1990) ³¹
Norway	1981-1994	1.6	5.5	Nystad et al (1997) ³²
Papua New Guinea	1973-1984	0.0	0.6	Dowse et al (1985) ³³
Scotland	1964-1989	10.4	19.8	Ninan and Russell (1992) ³⁴
Singapore	1967-1994	4.0	20.0	Lee et al (1997) ³⁵
Sweden	1971-1981	1.9	2.8	Alberg (1989) ³⁶
Tahiti	1979-1984	11.5	14.3	Liard et al (1988) ³⁷
Taiwan	1974-1985	1.3	5.1	Hsieh and Shen (1988) ³⁸
United States	1971-1976	4.8	7.6	Gergen et al (1988) ³⁹
	1981-1988	3.1	4.3	Weitzman et al (1992) ⁴⁰
Vietnam	1961-1991	2.1	7.6	Nguyen (1995)*
Wales	1973-1988	4.2	9.1	Burr et al (1989) ⁴¹

Asthma or asthma symptom prevalence data for a country are only included if the same method was used on two occasions. Many different methods were used to define asthma or asthma symptoms in studies from the different countries; as a result, comparison of the asthma prevalence rates between countries should be avoided.

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this pattern was unexplained, it appeared unlikely to be caused by translation problems. This interpretation is supported by their subsequent observation that English-speaking populations also had the highest prevalence of "atopy," defined as the presence of at least one elevated allergen-specific IgE.⁴³

These patterns are also consistent with the preliminary ISAAC study findings, in which the highest prevalence rates were observed in centers from the British Isles, Australia, New Zealand, and the Republic of Ireland. Importantly in the ISAAC program, the overall pattern of international differences between English and non-English-speaking countries observed with the written questionnaire were maintained in the video questionnaire, suggesting that these were unlikely to be caused by translation or interpretation problems (Table V).¹⁶ Thus while differences in language or labeling of symptoms such as wheeze may contribute in part to the observed international differences, they are unlikely to explain the substantial international differences in the prevalence of asthma between English-speaking and non-English-speaking countries seen with both the written and video questionnaires.

Asthma prevalence is increasing in developing countries as they become more Westernized or become urbanized

The fourth key pattern is that asthma prevalence is increasing in developing countries as they become more

TABLE IV. ISAAC: Prevalence of self-reported wheeze in last 12 months in 13- to 14-year-old children from centers in countries from the Southeast Asian region (%)

	Written questionnaire Wheeze (any)	Video questionnaire Wheeze (at rest)
China	3.1-5.1	1.3-3.3
Taiwan	4.2	5.7
Malaysia	6.8-8.9	3.8-5.3
Philippines	12.3	9.6
Singapore	12.3	n/a
Hong Kong	12.4	10.1
Japan	13.2	10.3

Westernized. For example, Hsieh and Tsai⁴⁴ examined the prevalence of allergic disorders in schoolchildren 7 to 15 years of age in Taipei, Taiwan, and found that the prevalence of childhood asthma increased from 1.3% in 1974 to 5.1% in 1985 and 5.8% in 1991.

Similar findings have been observed when communities move from a rural to an urban environment. The magnitude of the increase in asthma prevalence that may occur with urbanization may be considerable. For example, in a study from the 1970s the prevalence of asthma among Xhosa children living in a Cape Town township was more than 20 times greater than those from a rural area in the Transkei.⁴⁵ Similar findings have been observed in a more recent study from Zimbabwe, in which exercise-induced asthma was used as a more

TABLE V. ISAAC: Prevalence of self-reported wheezing in the last 12 months in 13- to 14-year-old children: Comparison of results obtained from written and video questionnaires according to languages used in different countries

Language	Prevalence (%)		
	English	Spanish	Chinese
Country	New Zealand	Spain	China
(No. of centers)	(6)	(5)	(5)
Written questionnaire	30.2	9.7	4.2
(wheeze, any)			
Video questionnaire	18.4	7.4	2.0
(wheeze at rest)			

objective marker of reversible airflow obstruction.⁴⁶ In this study, 25- to 50-fold differences between rural and urban populations were observed, findings that could not be accounted for by genetic factors.

The prevalence of other allergic disorders is also increasing worldwide

The fifth pattern is that the prevalence of other allergic disorders such as allergic rhinitis, atopic eczema and urticaria are also increasing worldwide.^{44,47,48} The magnitude of these increases is similar to that occurring with asthma prevalence, although the time course has been observed to be different, with the increase in asthma prevalence predating by at least 10 years the increase in allergic rhinitis and atopic eczema.⁴⁴

WHAT DOES THIS TELL US ABOUT THE MAJOR CAUSES OF ASTHMA WORLDWIDE?

These features of the international patterns of asthma prevalence raise major issues regarding current knowledge of the causes of asthma worldwide. In particular, it is evident that the current recognized risk factors for the development of asthma probably cannot fully account for either the worldwide increase in prevalence or the international variations in asthma prevalence that have been observed.

For example, the global pattern of asthma prevalence is consistent with the considerable body of evidence that air pollution is not a major risk factor for the development of asthma. Regions such as China and Eastern Europe, where some of the highest levels of traditional air pollution such as particulate matter and SO₂, generally have lower asthma prevalence than the countries of Western Europe and North America, Australia, and New Zealand, which have lower levels of pollution. It also appears unlikely that the international prevalence patterns can be explained by differences in smoking. This is illustrated by the study of Chinese communities living in the Southeast Asian region, in which the lowest prevalence of asthma was observed in the community living in mainland China, despite the highest level of cigarette consumption.⁴⁹

Furthermore, although sensitization to the house dust

mite allergen is an important risk factor for the development of asthma,⁵⁰ and there is some evidence that "Westernization" may increase levels of exposure to house dust mites, this appears unlikely to explain the international prevalence patterns. For example, Lai⁵¹ reported that levels of house dust mite allergen were very similar in houses in Hong Kong and Guangzhou despite the considerable difference in asthma prevalence. Furthermore, recent studies from both China⁵² and Africa⁵³ have shown that marked differences in asthma prevalence may occur in populations despite similar rates of atopic sensitization. These findings support the view that in addition to atopic sensitization, other risk factors may be important in the development of asthma in susceptible populations. In addition, other factors (independent of allergen levels) may affect the susceptibility to sensitization.

As a result of these major anomalies in the international asthma prevalence patterns, recent research has focused not only on "established" risk factors such as allergen exposure, but also on other factors that may "program" the initial susceptibility to sensitization or contribute to the development of asthma independent of atopic sensitization. For example, it has recently been identified that a large head circumference at birth is a risk factor for the subsequent development of asthma during childhood⁵⁴ or atopy in adult life.⁵⁵ Although the reasons for this association are unclear, it is known that head circumference at birth reflects a number of intrauterine factors, particularly those relating to maternal nutritional status and placental function. This is an intriguing finding as asthma prevalence has increased in many countries as the nutritional status (and head circumference at birth) has increased, raising the possibility that fetomaternal nutritional status may lead to programming of the developing immune or respiratory system, predisposing to the subsequent development of asthma.

There is also evidence that a small family size is associated with an increased risk of development of asthma.^{56,57} The reasons for this are unclear, but a similar relation with atopy has been observed in several studies,⁵⁸⁻⁶⁰ and it has been suggested that small family size could reduce infections in infancy and that this could in turn increase the risk of atopic disease at older ages. In support of this hypothesis is the observation that infections may downregulate production of IgE⁶¹; this may be why measles infections have been found to protect against atopy in Guinea-Bissau,⁶² positive tuberculin responses have been found to protect against atopy in Japan,⁶³ and hepatitis A infections were found to protect against atopy in Italy.⁶⁰ Finally, it is also possible that immunization may contribute to the development of asthma and atopy, whether through reducing clinical infections in infancy or through the direct IgE inducing effects of the vaccines themselves and/or the potentiating adjuvants.^{64,65}

SUMMARY

Asthma epidemiology is entering a phase of major significance that is likely to lead to greatly increased under-

standing of the causes of asthma. A key contributor to this increased understanding is the evidence from international comparisons of asthma prevalence, particularly those from the ECRHS study of asthma prevalence in adults and the ISAAC study of asthma prevalence in children. Although the findings of these two major international studies had not been fully published at the time of preparation of this report, considerable information is still available from the published results to date together with other asthma prevalence studies. It is therefore possible to draw some tentative conclusions as to the patterns of asthma prevalence worldwide. There are five striking patterns in this respect. First, asthma prevalence is increasing worldwide; second, asthma is generally more common in Western countries and less common in developing countries; third, asthma is more prevalent in English-speaking countries; fourth, asthma prevalence is increasing in developing countries as they become more Westernized or communities become urbanized; and fifth, the prevalence of other allergic disorders may also be increasing worldwide. These five key features of the international patterns of asthma prevalence raise major questions about the role of "established" risk factors for the development of asthma. As a result, recent research has expanded to include the study of novel factors that may "program" the initial susceptibility to sensitization or contribute to the development of asthma independently of atopic sensitization. These include various exposures in utero that are reflected in various perinatal factors measured at birth and exposure (or lack of exposure) in the early years of life that may make the infant more susceptible to the subsequent development of asthma. These issues are now the focus of an intensive research effort worldwide and the next few years are likely to see exciting advances in our understanding of the causes of asthma.

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